Class II Special Controls Guidance Document: Human Dura Mater; Draft Guidance for Industry and FDA

Draft Guidance – Not for Implementation

This guidance document is being distributed for comment purposes only.

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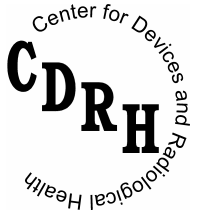
When final, this document supersedes "Guide for the Preparation of a Premarket Notification Application for Processed Human Dura Mater" dated October 14, 1999.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Plastic and Reconstructive Surgery Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation

Preface

Public Comment:

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852.

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This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

1. Purpose

This draft guidance document was developed as a special controls guidance to support the classification of the human dura mater device into class II. The device, as proposed, is intended to repair defects in the dura mater. This draft guidance will be issued in conjunction with a Federal Register notice announcing the proposal to classify this device type. This guidance is issued for comment purposes only. If a final rule to classify this device type is not issued, this guidance document will not be issued as a special control.

When final, this draft guidance document will supersede the "Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater" dated October 14, 1999.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of human dura mater. Thus, a manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the Act), including the 510(k) requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with human dura mater identified in this guidance and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device, unless exempt from the premarket notification requirements of the Act (refer to 21 CFR 807.85).

This special control guidance document identifies the classification regulations and product codes for the human dura mater (Refer to Section 5 – **Scope)**. In addition, other sections of this special control guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these human dura mater and lead to a timely 510(k) review and clearance. This document supplements other agency documents regarding the specific content requirements of a 510(k) submission. You should also refer to 21 CFR 807.87 and other agency documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, http://www.fda.gov/cdrh/manual/510kprt1.html.

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial**

Equivalence in Premarket Notifications; Final Guidance[1]," a manufacturer may submit a traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once a Class II Special Controls Guidance Document has been issued. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special control guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this guidance document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 807.87 as well as some other items that we recommend you should include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this Class II Special Controls Guidance Document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 12 for specific information that we recommend including in the labeling for devices of the types covered by this guidance document.)

Summary report

We recommend that the summary report contain:

- Description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. You should also submit an "indications for use" enclosure.[2]

- Description of device design requirements.

- Identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to Section 6 for the risks to health generally associated with the use of this device that FDA has identified.)

[1] http://www.fda.gov/cdrh/ode/parad510.html
[2] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

- Discussion of the device characteristics that address the risks identified in this Class II Special Controls Guidance Document, as well as any additional risks identified in your risk analysis.

- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 7-11 of this Class II Special Controls Guidance Document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

- If any part of the device design or testing relies on a recognized standard, (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.[4] Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. (21 USC 514(c)(2)(B)). For more information, see FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

If it is not clear how you have addressed the risks identified by FDA or through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how we recommend that you apply this Class II Special Controls Guidance Document to a premarket notification for a human dura mater.

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[3] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria, and thus differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[4] See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

4. Human Dura Mater

A. Human Dura Mater and Creutzfeldt Jakob Disease

- In February 1987, the Center for Disease Control and Prevention (CDC) reported the first U.S. case of Creutzfeldt Jakob Disease (CJD) in an individual who had received a human dura mater graft. CJD is a rare, invariably fatal degenerative disease of the central nervous system characterized by progressive dementia. In 1996, a nationwide CJD survey in Japan identified 43 cases associated with implantation of processed human dura mater. This increased the worldwide total of published cases of CJD associated with human dura mater use to 62. The great majority of these cases (59 out of 62) were related to the use of Lyodura, a particular brand of human dura mater manufactured in Germany. It should be noted that Lyodura was never cleared for commercial distribution in the U.S. and the import alert issued by FDA in June 1987 for this product continues to be in effect as of the publication date for this guidance.

- In March 1997, the World Health Organization (WHO) recommended that human dura mater grafts no longer be used, especially in neurosurgery, unless no alternative was available. At the same time, the Japanese Health and Welfare Ministry banned the use of human dura mater in brain surgery in Japan.

- Because FDA established safeguards and guidelines in 1990 in an effort to minimize the possibility of CJD transmission by human dura mater device implantation and because there were no confirmed cases of CJD-transmission related to the use of human dura mater that was legally cleared for U.S. commercial distribution as of March 1997, the FDA did not restrict the distribution of human dura mater in the United States. However, the decision was made to hold public meetings of the FDA Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) to re-evaluate the safety of human dura mater grafts with respect to surgical use and CJD transmission.

- On October 6, 1997, the TSEAC met to consider information provided by the FDA, industry, CDC, National Institutes of Health (NIH), the neurology medical community, and other internationally recognized experts and make recommendations concerning the clinical benefits and risks of CJD transmission associated with human dura mater grafts. At the conclusion of this meeting, the TSEAC recommended unanimously that neurosurgeons should avoid the use of human dura mater whenever possible. The committee also concluded, however, that the final decision regarding use of human dura mater should be left to the discretion of the treating neurosurgeon, as long as the human dura mater is procured and processed following certain safety measures.

- Based upon the TSEAC's recommendations, on March 6, 1998, FDA sent letters to suppliers of human dura mater requesting that they implement specific measures to improve the safety of human dura mater.

- At the April 16, 1998 TSEAC meeting, FDA presented proposed revisions to the TSEAC's recommendations offered during their October 6, 1997 meeting. These revisions took into consideration the responses from the human dura mater suppliers to the FDA letter of March 6, 1998. Those sponsor's responses raised concerns about the feasibility or necessity of some of the recommendations. Transcripts for TSEAC meetings are available at http://www.fda.gov/cber/advisory/tse/tsearchives.htm.

- On January 18-19, 2001, the TSEAC also discussed criteria for determining the suitability of donors of human cells, tissues, and cellular and tissue-based products with regard to CJD and variant CJD (vCJD). The recommendations provided by the TSEAC at this meeting are also incorporated into this revised guidance document.

- The recommendations and guidance presented in this document also considered the issues raised in a citizen petition to ban and recall all human dura mater devices that was submitted to FDA on August 15, 2001, by Public Citizen.

- While reagents for proteinase-resistant prion protein (PrP-RES) testing of brain tissue are available from certain research laboratories, testing is currently a research/investigational-use tool (Ref. 1). Because there is no FDA-approved or validated PrP-RES test that is marketed for screening donors for CJD, the FDA is not advocating its use at this time. However, when either a validated test becomes available or evaluation of available data demonstrates the utility of PrP-RES testing as an aid in determining that brain and dura mater tissues are not contaminated with CJD, incorporating PrP-RES testing into standard operating procedures will be recommended.

B. Regulatory Authority

- Although not the primary purpose of this guidance document, FDA would also like to clarify the regulatory history of human dura mater. Human dura mater was in commercial distribution before the enactment of the Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act. The Neurological Devices Advisory Panel (the Panel) initially made a classification recommendation at the February 2, 1990 meeting. Because product classification was not finalized and new information about the safety of this device became available during the following nine years, FDA requested a second classification recommendation from the Panel on September 16, 1999. Regulation as a class II medical device was recommended at both Panel meetings. As of the date of issuing this guidance, processed human dura mater products continue to be regulated as unclassified medical devices via premarket notification.

- In February 1997, FDA proposed a risk-based approach to the regulation of human cellular and tissue-based products (Ref. 2). To implement the proposed approach, FDA has published three proposed rules. "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing; Final Rule" has been finalized (Ref. 3). The two proposed rules "Suitability of Donors of Human Cellular and Tissue-Based Products; Proposed Rule" (Ref. 4), and "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Proposed Rule" (Ref. 5), are in the process of being finalized.

- FDA will redesignate the regulation of human dura mater from the medical device authorities to the human tissue regulations under the legal authority of Section 361 of the Public Health Service Act. However, the precise date of this transfer is dependent upon finalization of the above cited rules for "Suitability of Donors of Human Cellular and Tissue-Based Products; Proposed Rule" and "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Proposed Rule."

- Thus, FDA believes that human dura mater that meets the criteria in Section 1271.10 of the "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" may be appropriately and effectively regulated solely under Section 361 of the Public Health Service Act by controlling the potential infectious disease risks posed by transplantation. However, because human dura mater products are currently regulated as medical devices and will continue to be so regulated until all the tissue rules are finalized, FDA is providing the information below to help 510(k) applicants submit sufficient information to demonstrate a reasonable assurance of the safety and effectiveness for these devices as described in 21 CFR 860.7(g)(2) (Ref. 6).

5. Scope

The scope of this document is limited to the human dura mater device, regulation number 21 CFR 882.xxxx (to be designated, if a final rule is published), and product code LEM. A human dura mater device is human pachymeninx tissue intended to repair defects in the dura mater.

§ 882.xxxx Human dura mater.

a. Identification. Human dura mater is human pachymeninx tissue intended to repair defects in human dura mater.

b. Classification. Class II (special controls). The special control for this device is FDA's "Class II Special Controls Guidance Document: Human Dura Mater; Guidance for Industry and FDA."

Human dura mater should not be confused with dura mater substitute devices, which are classified under 21 CFR 882.5910, product code GXQ.

6. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the human dura mater addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk

analysis, prior to submitting your 510(k), to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this guidance document, or have identified risks additional to those in the guidance, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Infection related to patient condition and treatment	Sections 7-11
Transmission of spongiform encephalopathies	Sections 7-10, 12
CSF leakage	Sections 9-10
Adverse tissue reactions	Sections 9-11

7. Donor Qualification

A. Serology Testing

A blood specimen from all potential donors should be tested and found negative for antibodies to pathogens of concern using FDA licensed or approved screening tests. Today that list includes the human immunodeficiency virus, Type 1 and Type 2 (anti-HIV-1 and anti-HIV-2), hepatitis B surface antigen (HBsAg), and antibodies to the hepatitis C virus (anti-HCV). Tests should be performed in a CLIA-certified laboratory. Screening tests that have been licensed for testing cadaveric blood should be used, when available.

B. Evaluating risk factors for, and clinical evidence of, neurological and infectious diseases through medical record review and donor history interviews

We recommend that each 510(k) describe the methods for evaluating the possible presence of risk factors for, and clinical or physical evidence of, neurologic or infectious disease. For example:

All available information, including a donor's medical records, autopsy reports, or any physical assessment reports (e.g., medical examiner report, police records) should be reviewed to determine donor suitability. These records should be evaluated by an individual who is qualified by profession, education, and training and who is familiar with the intended use of human dura mater.

Interviews should also be performed with one or more individuals who can provide reliable information (e.g., a donor's next of kin, a relative, a member of the donor's household, an individual with an affinity relationship with the donor, or the donor's primary treating physician) concerning the donor's medical history and relevant social behavior. The interview should determine whether the donor had signs or symptoms of neurologic disease or engaged in certain activities or behaviors that place a donor at a high risk for HIV or hepatitis infection.

The interview should also seek to determine whether the potential dura mater donor traveled or resided in a BSE-identified country during the time and for a duration that would defer an individual as a blood donor. CBER's blood donor selection criteria regarding CJD are described in the "Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood

Products" (Ref. 7). FDA believes that applying the blood donor selection criteria when considering potential human dura mater donors is appropriate given the current lack of information available about the incidence and transmissibility of vCJD.

The manufacturer should establish donor selection criteria and develop standardized methods for reviewing medical records and performing interviews. Such procedures should draw upon the appropriate standards of voluntary organizations (e.g., American Association of Tissue Banks and Eye Bank Association of America) as well as the recommendations, guidelines, and regulations of Public Health Service agencies (Refs. 8-17).

We recommend that exclusion criteria include, but not be limited to, the following:

Regarding neurological screening

- donors diagnosed with CJD or a known family history (blood relative) of a person with non-iatrogenic CJD
- donors who received injections of human pituitary-derived growth hormone (pit-hGH)
- donors who received transplants of dura mater
- donors diagnosed with any degenerative or demyelinating disease of the CNS (e.g., multiple sclerosis) or other neurologic diseases (e.g., senile dementia, Alzheimer's disease)
- donors who died in a neurological/psychiatric hospital.

Other exclusion criteria

- donors who meet the exclusion criteria for potential infectious disease described in the "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation" (Ref. 15)
- donors diagnosed with active infections at the time of death (e.g., rheumatic fever, generalized septicemia or systemic infection, mycosis, tuberculosis)
- donors diagnosed with diseases of unknown etiology
- donors without adequate documentation of medical history.

C. Physical Assessment

The 510(k) should identify standardized donor selection criteria for physically assessing a cadaver in a general autopsy. Exclusion criteria based on clinical evidence of possible infectious or neurologic diseases should include, but not be limited to, evidence of:

- physical evidence for risk of sexually transmitted diseases, such as genital ulcerative disease, herpes simplex, and syphilis
- physical evidence of anal intercourse, including perianal condyloma
- physical evidence of non-medical percutaneous drug use, such as needle tracks
- disseminated lymphadenopathy
- oral thrush
- blue or purple spots consistent with Kaposi's sarcoma
- needle tracks, including examination of tattoos which may be covering needle tracks
- unexplained jaundice, hepatomegaly, or icterus
- if the body was rejected for routine autopsy due to infectious criteria or if the autopsy was done in an infectious disease control room or under any special precautions and the reasons for these procedures.

D. Gross and Histological Examination of the Brain

The 510(k) should describe the procedures for performing a full autopsy on each donor's brain. Following fresh examination, the brain should be fixed, sliced, gross examination of the entire brain conducted, including multiple cross sections, and multiple samples of tissue obtained from different parts of the brain for histologic examination. This examination should be performed by a qualified pathologist after human dura mater collection. Potential donors should be excluded when any possible evidence of TSE-related changes is observed during gross and histological examination of the brain (Refs. 1, 18-20).

E. Archiving of Donor Brain and Dura Mater Tissue

FDA recommends that frozen (at a temperature equal to or less than -70°C) and fixed samples of both donor brain and dura mater tissues should be archived. The donor brain samples should include at least 5 grams of the frontotemporal region.

These samples should be retained for 10 years based on the current scientific knowledge regarding the development of screening tests and our expectation that, as the science evolves, screening tests may become available within that time.

While archiving samples of donor brain and dura mater may not immediately increase the assurance of dura mater graft safety, comprehensive collection and storage of such tissues would permit subsequent testing for TSE-induced changes when improved or new test methods become available. In the event that a human dura mater-graft recipient becomes ill with CJD, testing of archival donor material might assist in determining whether the dura mater graft was the source of infection.

8. Qualification of Other Components

The source and purity of all other components and manufacturing materials (e.g., preservatives) should be identified in the 510(k). Such information may be supplied by reference to a Master File(s) if a letter of cross-reference is included which authorizes FDA review of the appropriate documents. Submission of a Certificate(s) of Analysis (CoA) and/or a Materials Safety Data Sheet(s) (MSDS) for each device component can also greatly simplify the 510(k) review.

9. Device Manufacturing: Processing Methods

A. Manufacturing Reagents

The 510(k) should contain information about all reagents (e.g., organic solvents) and processing methods used in device manufacture. Information similar to that discussed above for device components, (i.e., reagent source, purity, CoA and/or MSDS) can be very helpful in evaluating the substantial equivalence of the proposed and legally marketed devices. The 510(k) should also identify the concentration in the final device of any manufacturing reagent that is potentially toxic.

B. CJD Disinfection

Careful control of donor selection and dura mater retrieval procedures constitute critical safety practices for human dura mater. While histological examination of the brain may detect most infected tissues, it may not identify all CJD-infected grafts. Therefore, treatment of each product with a generally accepted disinfection technique should be performed to provide an additional assurance of device safety. The TSEAC recommended treating human dura mater with 1.0 N sodium hydroxide (NaOH). This recommendation was based on a study in an animal model in which 1.0 N NaOH treatment reduced CJD infectivity (Ref. 18). Each application should provide information about the methods for disinfection with NaOH or another procedure that has been validated to significantly reduce CJD infectivity. Such data should also demonstrate that subsequent rinsing steps are sufficient to reduce the concentration of residual NaOH (or another disinfectant) to a non-cytotoxic level and that the human dura mater retains its clinical utility.

10. Device Manufacturing: Manufacturing Controls

Because product specifications and end-product testing alone are insufficient to control critical characteristics of this product, the manufacturer should carefully monitor donor selection, tissue collection procedures, device processing, packaging, and distribution to achieve a reasonable assurance of product safety. The 510(k) should provide evidence that sufficient controls for device manufacture are in place to assure the safety of the final product. The manufacturer should provide the following information about manufacturing controls:

A. Excision Procedures

Written procedures should require aseptic conditions for handling of all tissues. Tissue recovery should be performed within 24 hours of death and with sufficient temperature control to limit the effects of autolysis.

B. Excision Facilities

The manufacturer should provide information concerning how the excision facility (morgue) meets the minimum standards of a surgical operating room. Such information should describe, but not be limited to, whether the excisional facility has:

- air filtration
- stainless steel furniture
- washable walls
- refrigeration for cadaver storage
- hypothermia blankets to cool the cadaver during the procedure
- single use or disposable instruments and processing aids for each donor.

C. Batch Processing

Human dura mater grafts from different donors should not be co-mingled during tissue collection or product manufacture. The 510(k) should describe efforts to eliminate opportunities for cross-contamination during tissue collection and processing as well as the procedures employed to prohibit batch processing of material from different donors. For example, procedures should require the use of only disposable processing materials and surgical instruments during the recovery and processing of dura mater allografts. Because FDA is unaware of any procedure or reagent that is validated to totally inactivate the CJD-causing agent, FDA would welcome any information that justifies an alternative approach to the sole use of disposable processing materials and surgical instruments.

D. Record Keeping/Tissue Tracking

As described in 21 CFR 820.60 subpart F, each manufacturer must establish and maintain procedures for identifying the product during all stages of receipt, production, distribution, and application. The 510(k) should describe the methods and record keeping procedures for tracking each lot of final product directly back to the tissue donor as it relates to donor medical records and device manufacturing records.

Although not required to be submitted as part of the 510(k), the manufacturer should maintain the following data as part of the donor medical records:

- the record of the time of death and certification of the time of tissue recovery
- the results of post-mortem examination and serological studies sufficient to evaluate the potential of communicating infectious, malignant, and/or neurological disease or to detect diseases of unknown etiology
- the record of compliance with the written procedures for recovery.

For additional information regarding device manufacturing records, the manufacturer should refer

to 21 CFR 820 subpart M (Quality System Regulations).

For additional information regarding the tracking regulation, the manufacturer should refer to 21 CFR 821 and Section 519(e) of the Federal Food, Drug, and Cosmetic Act), which was issued on December 14, 1998. A manufacturer should also refer to "Guidance Document on Medical Device Tracking (1999)" for additional information on procedures for accurately tracking medical devices.

11. Final Sterilization

For devices labeled as sterile, a sterility assurance level (SAL) of 10^{-6} is recommended. All sterility data should be obtained by methods consistent with a recognized standard or guidance for assessing the ability of the manufacturing and sterilization processes to inactivate bacteria, fungi and yeast (e.g., **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/361.html). In addition, the manufacturing methods should demonstrate that the sum of the log clearance of virus from manufacturing and sterilization processes are at least six logs greater than the concentration of virus anticipated in the unprocessed source material. Studies determining the viral inactivation properties may be performed with on selected scaled down versions of specific manufacturing and the sterilization processses using appropriate model viruses. FDA recommends review of the "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (Ref. 21) for information about the design of such studies and the selection of model viruses.

Regarding final sterilization procedures, the 510(k) should describe:

- the method of sterilization
- the validation method for the sterilization cycle
- the SAL to be achieved
- the method for monitoring the sterility of each production lot.

If radiation sterilization is used, the sterilizing dose and methods for monitoring exposure level should be specified. If ethylene oxide (EtO) sterilization is performed, the application should describe the methods by which residual levels of ethylene oxide, ethylene chlorohydrin, and ethylene glycol are determined and the amount of EtO and residues remaining on/in the device. Because EtO and its decomposition products may be very neurotoxic, specifications for EtO residuals should be set at a non-cytotoxic level. Review of "Guidance for ANSI/AAMI/ISO 10993-7: 1995, Biological evaluation of medical devices-Part 7: Ethylene oxide sterilization residuals" is recommended.

12. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e).[5]

Prescription Device

In accordance with 21 CFR 801.109, this device must bear the following caution statement: "Caution: Federal law restricts this device to sale by or on the order of a physician."

Graft

The labeling should include information so that the graft recipient is notified in writing that she/he has received a human dura mater graft implant.

Tissue Sourcing

The labeling should permit information on tissue sourcing to be maintained in the recipient's hospital record.

Alternatives

Because the WHO and the TSEAC have stated potential concerns related to potential CJD and vCJD transmission, product labeling should remind practitioners to consider the risks and benefits of human dura mater implantation, including the use of alternative products and procedures.

[5] Although final labeling is not required for 510(k) clearance, final labeling must also comply with the requirements of 21 CFR 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of part 801.

References

1. Kretzschmar, H.A., Ironside, J.W., DeArmond, S.J., and Tateishi, J., "Diagnostic Criteria for Sporadic Creutzfeldt-Jakob Disease," *Arch. Neurol.* 1996; **53**:913-920.

2. "Proposed Approach to Regulation of Cellular and Tissue-Based Products" - 2/28/97. http://www.fda.gov/cber/gdlns/CELLTISSUE.pdf.

3. "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" (66 FR 5447, January 21, 2001), available at http://www.fda.gov/cber/guidelines.htm.

4. "Suitability Determination for Donors of Human Cellular and Tissue-Based Products" (64 FR 52696, September 30, 1999).

5. "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement" (66 FR 1508, January 8, 2001).

6. "The Commissioner may require that a manufacturer, importer, or distributor make reports or provide other information bearing on the classification of a device and indicating whether there is reasonable assurance of the safety and effectiveness of the device or whether it is adulterated or misbranded under the act." (21 CFR 860.7(g)(2))

7. "Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products," 8/27/01, available at http://www.fda.gov/cber/gdlns/cjdvcjd.htm.

8. FDA Recommendations to Blood Establishments for "The Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg)," 12/2/87.

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